Cardiac Transplantation in Hawaii

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Clinical cardiac transplantation was successfully introduced 26 years ago, and from an initial experimental status, it has moved forward to become an accepted and well-established treatment modality for end-stage cardiac disease. The first cardiac transplant operation in Hawaii was performed in March 1987; the patient lived for 1 year. A total of 20 heart transplant operations have been performed in 19 patients at St. Francis Medical Center in Honolulu. There has been only one hospital death, and our current one-year survival is 77%, which is similar to national statistics. Our longest survivor is now more than 6 years following transplantation. The incidence of rejection episodes and infectious complications is comparable to other studies.

Introduction

Following successful animal experiments in the late 1950s, cardiac transplantation was applied clinically for the first time in 1967. This event led to an unwarranted rush of transplant operations worldwide with resulting poor outcomes. It was through the meticulous efforts of the Stanford group with steadily improving results in the 1970s that transplantation of the heart regained prominence as a valuable procedure in the treatment of end-stage cardiac disease. With the introduction of cyclosporine as part of the immunosuppressive regimen in 1980, a new higher level of success was achieved that produced the appearance of many new transplant programs. The surgical techniques and immunosuppression protocols have become standardized with expected good results. This report reviews the experience with heart transplantation in Hawaii since its inception in 1987.

Patients and methods

After months of preparation, the first cardiac transplant operation in Hawaii was performed in March 1987[1]. Since that time, a total of 20 operations have been performed in 19 patients. The selection of patients was based on standard criteria: All were in advanced cardiac failure and had no other alternative treatment. There were 17 men and 2 women who were aged 23 to 60 years old (mean 40). Seventy-four percent of these patients (14/19) had idiopathic dilated cardiomyopathy. Five patients had undergone previous cardiac surgery; one patient had 3 previous coronary bypass operations and the placement of an AICD. For patients who were discharged from the hospital, the length of stay varied between 14 and 74 days, with an average of 24 days. The operations were performed between March 1987 and May 1993, and the follow up was completed in December 1993. A profile of the recipient patients is seen in Table 1.

Our immunosuppression regimen has been modeled after the Stanford University protocol and consisted of triple drug oral therapy (cyclosporine, azathioprine and prednisone) plus induction with the monoclonal antibody OKT3 for 14 days. All patients had routine surveillance cardiac biopsies weekly after transplantation for the first 6 weeks, biweekly for 2 months, and monthly until 6 months following the operation. Thereafter, they were biopsied every 3 months for life. Once a year, full cardiac catheterization and coronary angiography were obtained.

Rejection was diagnosed in asymptomatic patients on routine biopsy using standard criteria and on symptomatic patients by clinical diagnosis plus echocardiogram and confirmed by urgent biopsy. Treatment of moderate or severe rejection consisted of 3 consecutive daily doses of 1 gram of methyl-prednisolone. If this failed to clear the episode, a second course of methyl-prednisolone or a repeat course of OKT3 was given. In the case of humoral rejection, characterized by the absence of cellular infiltrates and severe cardiac failure, plasmapheresis or immunoadsorption columns (ProSorba®) were used. This consisted of daily treatments for 3 days, followed by 3 more treatments every other day. In patients who rejected several months after transplantation, the episode was treated with high dose oral steroids (prednisone 50 mg twice a day for 3 days) with tapering over 2 weeks.

Infection surveillance was very strict. All patients (recipients and donors) were screened for CMV IgM and IgG, hepatitis, toxoplasmosis and HIV. After transplantation, routine cultures of sputum and urine were obtained twice a week. Weekly specimens of urine, throat secretions, and blood were obtained for CMV cultures. Appropriate cultures were repeated when clinically indicated.

Donor management was directed by the transplant surgeons.

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Hemodynamic stability was emphasized with particular interest in maintaining adequate intravascular volume, minimal inoptropic support with no more than 5 mcg/Kg/min of dopamine and acceptable oxygenation.

Brain death in 14 of the 20 donors was caused by head trauma; 5 had spontaneous intracranial hemorrhage, and 1 had a malignant brain tumor (Table 2). Donor age varied from 14 to 50 years old with a mean of 28. There were 17 men and 3 women; adequate recipient=donor matching included blood type (Table 1) and body size, with discrepancies in body weight no larger than ± 20%, if possible. No prospective tissue typing or crossmatching was performed. Before final acceptance of a donor heart for transplantation, it was required to have had a stable hemodynamic course, a normal or acceptable LV function by echocardiogram, and satisfactory contractility by visual inspection after opening the chest. Pulmonary artery pressure and cardiac output measurements, via Swan Ganz catheter, were performed when clinically indicated. Cardiac catheterization and angiography were done if donors were older than 45 years of age, or if they had a history of hypertension, heavy smoking, or prior heart disease. Standard surgical techniques were used for organ procurement and graft implantation. All transplanted hearts were placed in an orthotopic position. None of the patients was mechanically assisted, either pulmonary or cardiac, at the time of transplantation. Three patients were hospitalized with moderate or severe congestive failure when donors became available. Another patient had been hospitalized for more than 2 months with refractory cardiac failure, requiring 3 weeks of intraaortic balloon (IABP) support, and complicated with a cerebrovascular accident. She recovered from this episode, was discharged home, and transplanted a few weeks later. All donors except 1 were from the Honolulu metropolitan area, and they were transferred to St. Francis Medical Center to decrease the ischemic time. One donor heart was procured in Maui and flown to Honolulu for transplantation.

Results

Survival/initial hospitalization. Operative mortality was 5%. Only 1 patient out of 19 died during the immediate postoperative period.

Long-term survival. The 1-year survival rate was 77%, at 3 years 70% of patients were alive, and 60% survived more than 5 years.

Functional results. All surviving patients except 1 became asymptomatic following transplantation. The patient who continued in failure was a very debilitated 60-year-old man who had 3 previous coronary bypass operations and was hospitalized with severe congestive heart failure and anasarca. He also had chronic pulmonary disease and following transplantation had a stormy course requiring re-exploration for bleeding, prolonged ventilatory support, and a tracheostomy. He was discharged after 73 days in functional class II. Currently more than 2 1/2 years following the operation, he still has moderate limitation in exercise tolerance. Ten of the 14 patients (71%) who survived more than 1 year were rehabilitated and went back to full- or part-time work, or full-time school. One patient retired voluntarily.

Cause of death. A total of 6 patients have died: One patient died during the initial hospitalization 4 days after the operation; 5 patients died 4 months to 26 months following transplantation. The only hospital death occurred in a 48-year-old woman who had early graft failure probably related to pulmonary hypertension (No. 2, Table 1).

Of the late deaths, 4 were due to rejection and 1 due to infection. The first transplant recipient died 12 months after transplantation from complications of rejection that resulted from non-compliance with the medical regimen. Severe rejection was the cause of death in 3 other patients; these occurred 7, 9, and 22 months following transplantation. The first of these patients (No. 13, Table 1) had an uncomplicated operation and was discharged after 21 days in the hospital. He subsequently had 3 episodes of rejection in the first 3 months, requiring intravenous methyl-prednisolone therapy. Seven months after the operation, he had an episode of upper respiratory infection and presented at another hospital with abdominal fullness and dyspnea. Work-up for intra-abdominal pathology delayed the diagnosis of rejection, and he presented to St. Francis Medical Center *in extremis* with cardiogenic shock. One gram of methyl-prednisolone was given at the other hospital before transfer. Total cardiopulmonary support (CPS ®) was provided, but it proved inadequate, with ongoing metabolic acidosis. The same day a donor heart became available and the patient was retransplanted, but could not be weaned from cardiopulmonary bypass and died. The second patient (No. 17, Table 1) had ongoing rejection since the transplant operation, and although clinically he did well for several weeks at a time, the protracted rejection which included alternating or combined humoral and cellular rejection, was never fully controlled despite multiple antirejection treatments. These included several courses of methyl-prednisolone, 3 courses of OKT3, 3 courses of plasmapheresis or immunoadsorption columns and a full course of total lymph node irradiation (80 cGy twice weekly for a total of 10 fractions or 800 cGy). He died 9 months after transplantation at home. The last of this group of patients (No. 11, Table 1) was admitted 26 months after transplantation with a severe episode of rejection and cardiogenic shock. He was placed on CPS 12 hours after admission, but continued deteriorating rapidly despite maximal support and died a few hours later. He is the only patient who has had documented severe 3-vessel coronary artery disease in the transplanted heart. This was known before death on his second-year routine coronary arteriogram, and confirmed at autopsy.

The patient who died of infection (No. 7, Table 1) had a prolonged re-admission to the hospital with disseminated CMV infection and an episode of severe rejection that was reversed with the help of CPS for 5 days. The ultimate cause of death was multiple organ failure from uncontrollable infection.

Morbidity

Infections. Infection episodes were relatively infrequent in our patients. Two episodes of successfully treated *pneumocystis carinii* pneumonia occurred in a patient 3 months and 11 months after transplant. One patient had disseminated CMV infection (previously discussed). Two other patients had systemic symp-

toms with elevated CMV titers and were treated with intravenous ganciclovir. Bacterial infections were seen infrequently and were never of life-threatening proportions. One episode of each of the following infections occurred at different occasions: Bacterial pneumonia, urinary tract infection, wound infection in a traumatic injury, and oral herpes. All of these episodes were adequately treated with the appropriate antibiotics.

Rejection. Of the 18 patients surviving the initial hospitalization, 13 patients (72%) suffered at least 1 episode of moderate acute cellular rejection requiring treatment during the first year. Of the remaining 5 patients, 2 rejected after 1 year, and 3 have never had episodes of rejection requiring therapy. As mentioned above, 3 patients had severe rejection that led to death, 2 within the first year, and 1 after 2 years. Humoral (vascular) rejection occurred in 3 patients at 2 weeks, 2 months, and 3 years following transplantation. These episodes were invariably severe and life-threatening with varying degrees of hemodynamic compromise. All 3 patients required admission to ICU and inotropic support, and 2 required IABP assistance. Treatment included high-dose methyl-prednisolone for 3 days and plasmapheresis and/or immunoadsorption columns. The initial episodes were reversed in all patients. One patient had recurrent rejection and eventually died of it (No. 17, Table 1. Discussed above). In the latest patient with humoral rejection, azathioprine was substituted with cyclophosphamide with good results. Graft atherosclerosis has been diagnosed by coronary angiography in 1 patient (2 years after transplantation) and confirmed as diffuse, severe 3-vessel involvement by autopsy after dying of rejection (See above). Another patient suffered an acute myocardial infarction several years after transplantation; there were EKG changes, but coronary angiography failed to reveal any obstructive lesions. Bradyarrhythmias occurred in 2 patients who responded adequately to oral theophylline. None of our patients has required implantation of a permanent pacemaker and none has developed malignant disease following transplantation.

Hospital cost

Information was available on the cost of the initial hospitalization of the last 9 transplant patients, all performed within the past 3 years. Excluding 2 patients, one with advanced debilitation who spent 2 1/2 months in the hospital following transplantation, and another patient who was hospitalized for 2 months before transplantation, the average hospital cost was $157,289. This reflects the expected current hospital cost for a relatively uncomplicated heart transplant operation excluding physician charges.

Discussion

Cardiac transplantation has achieved an important position in the therapy of incurable cardiac disease. Results have been consistently good since the advent of improved immunosuppressive methods. With the introduction of cyclosporine in 1980, the survival rates improved substantially from 63% to 80% at 1 year, and from 36% to 60% at 5 years.[2] The number of transplant centers and operations have increased remarkably in the past decade and the number of cardiac transplant operations worldwide increased from 700 in 1984 to 2,709 in 1992. A peak was reached in 1990 with a total of 3,289 operations.[3] Although the considerable increase in the number of operations is encouraging, the number of transplant operations remains limited by the availability of donors. Nearly 3,000 patients are waiting for donor hearts at any given time in the United States alone. Xenotransplantation will have to wait until greater advances in immunology take place, and it probably won't be a clinical reality within the next decade.

Selection criteria for recipients continue to evolve, however, the initial guidelines set by the Stanford group have remained mostly unchanged: The age limit is 60 years old, individualized consideration can be given to older patients if they are otherwise deemed good candidates. The oldest transplanted patient entered in the Registry of the International Society of Heart and Lung Transplantation was 75 years old[3] —newborns have been transplanted hours after birth. All candidates must have end-stage cardiac disease untreatable by other means with life expectancy measured in months, and a normal pulmonary vascular resistance (ideally < 3 Wood units). They should have normal or minimally affected kidney and liver function and have strong family support and good compliance, since the medication regimen, and infection and rejection surveillance are very stringent. Contraindications include any active infection, peptic ulcer disease, recent pulmonary embolism, current malignancy, insulin dependent diabetes mellitus and positive serology.

Operative mortality rates have remained steady at 8% to 10%[3]. We had a 5% mortality rate (1/19) and none of the last 17 patients has died during the initial hospitalization. Long-term survival rates are usually reported at yearly intervals with 1-, 5-, and 10-year survival rates used to compare results. Stanford reports an 80.7% and 59.7% 1- and 5-year survival rates for patients treated in the cyclosporine era (1980 to 1989)[2]. The same statistics are 79.1% and 67.8% reported by the Registry[3]. In the latter report, the 10-year survival rate was 55.8%. The survival rates at 1, 3, and 5-year intervals of 77%, 70%, and 60% in our program are similar to other reports.

It is unquestionable that cardiac transplantation has a profound effect in patients who are terminally ill and who would otherwise have a very limited life expectancy. Not only can this procedure add years to their lives, but, equally important, the majority of patients become fully rehabilitated and can enjoy productive lives. Seventy percent of our patients were able to go back to work or school. Similar functional results are reported from other institutions.[2]

In any organ transplantation, a narrow margin between infection and rejection is ever-present. Excessive immunosuppression will decrease the rejection rates, but it will increase the incidence and severity of infections. Deficient immunosuppression will result in fewer infection episodes, but the incidence of rejection will increase. Until better immunosuppressive drugs become available, we have to accept these potential complications and treat them with the best means available. Both infection and rejection remain the main causes of morbidity and mortality in transplant patients. As evidenced in our report, the majority of patients had at least one episode of rejection, and 5

Table 1 Characteristics of Transplant Recipients

No.	Age	Sex	Diagnosis	Blood Type Rec Donor	Previous Surgery	Length of Stay	Outcome
1	50	M	IDCM	A O	—	23	Died 1 year
2	38	M	IDCM	B O	—	18	Alive 6 years 4 months
3	48	F	IDCM	O O	—	4	Died 4 days
4	23	M	IDCM	A A	—	35	Alive 5 years 6 months
5	42	M	IDCM	A O	—	24	Alive 5 years
6	40	M	IDCM	O O	—	41	Alive 4 years 6 months
7	25	M	LVA	O O	Aneur resect	18	Died 4 months
8	34	M	IDCM	A O	—	21	Alive 3 years 9 months
9	23	M	IDCM	A O	—	18	Alive 3 years 6 months
10	56	M	CAD	A O	CABG	16	Alive 3 years 3 months
11	34	M	IDCM	A A	—	17	Died 2 years 2 months
12	60	M	CAD	O O	3 CABGs	74	Alive 2 years 8 months
13	32	M	IDCM	A O	—	21	Died 7 month after retransplantation
14	56	M	IDCM	O O	—	19	Alive 1 year 10 months
15	56	F	IDCM	B O	—	18	Alive 1 year 6 months
16	32	M	AR	O O	AVR	19	Alive 1 year 4 months
17	31	M	IDCM	B O	—	14	Died 9 months
18	54	M	AR	O O	AVR	24	Alive 13 months
19	37	M	IDCM	AB A	—	16	Alive 7 months

IDCM=Idiopathic Dilated Cardiomyopathy, **LVA**=Left Ventricular Aneurysm, **CAD**=Coronary Artery Disease, **CABG**=Coronary Artery Bypass Grafting, **AR**=Aortic Regurgitation, **AVR**=Aortic Valve Replacement

of 6 deaths were caused by or associated with rejection episodes. Typically, cellular rejection is discovered by routine biopsy in patients who are asymptomatic. Treatment with short-term enhanced immunosuppression with high-dose steroids aborts the episode and no long-lasting heart damage is seen. Recently, more serious rejection events have been seen. These are humorally mediated and typically present with sudden congestive failure symptoms which rapidly may advance to cardiogenic shock. These episodes are clearly life-threatening and a very aggressive approach is needed to reverse these events. Three of our patients have had such complications. Emergency biopsy has revealed little or no cellular infiltrates and may show vasculitis. Severe cardiac dysfunction is evident by clinical symptoms and signs and echocardiogram usually confirms the degree of impairment of left ventricular contractility. All 3 patients required inotropic medications to sustain cardiac function: 2 of the patients required mechanical assistance with IABP, 1 of them on 2 different occasions. The biopsy has not always been helpful, but when the combination of clinical findings is seen, immediate treatment is given. We have reversed all such episodes with the combination of high dose methyl-prednisolone and treatment with plasmapheresis or immunoadsorption columns. The immunoadsorption columns are used to remove circulating immunoglobulins in a selective manner rather than exchanging

Table 2 Donors. Cause of Brain Death

Head Trauma	MVA	8
	GSW	5
	Fall	1
Intracranial Bleeding		5
Brain Tumor		1

MVA=Motor Vehicle accident
GSW=Gunshot Wound

the whole plasma volume as plasmapheresis does. This treatment modality has been used in the recent past, and there are no reports with large experiences available. We have shown that it is an effective way of treating this devastating complication. In one patient, we stopped the azathioprine and substituted it with cyclophosphamide which has more specific effect on the antibody production limb of the immune response. This change seems to have controlled the humoral rejection in a better way.

A serious problem in long-term survivors is the appearance of graft coronary atherosclerosis. Stanford reports a 25% incidence at 5 years,[2] and it seems to correlate with CMV infections. Currently, there is no effective way of preventing this complication. The only effective treatment once it is advanced is retransplantation. Fortunately, we have not seen this problem frequently in our patients. Only one patient has had significant coronary artery obstruction which had no clinical manifestations.

Infectious complications have not been a major problem in our patient population. It is well known that opportunistic infections, mostly fungal and viral, are prevalent in transplanted patients. With one exception, all infectious episodes have been adequately treated.

Cardiac transplantation is an expensive procedure. Nonetheless, studies have shown this operation to be cost-effective. It is clear that most patients with end-stage cardiac disease are disabled, many of them being unable to work with resultant loss of income, and others have repeated or prolonged hospitalizations with accumulating health care costs. A transplant operation often reverses this downhill trend and can return the patient to a functional status. The results are not optimal yet and further improvements are expected as more experience accumulates, but great advances have been made in the past 3 decades. This endeavor requires a monumental effort from different institutions and many individuals. The main reward that professionals involved in transplantation receive is seeing a patient recover from a devastating disease.

Addendum

Since the completion of this study, one more patient, our longest survivor (who lived more than 6 years) died in January 1994. The cause of death has not been determined, however his death does not alter the 1-year, 3-year or 5-year survival statistics.

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Allogenic and Autologous Bone Marrow Transplant Experiences in Hawaii

➤ *Continued from page 73*

The Hawaii BMT program also has been investigated by NMDP. Approval has been given for St. Francis Medical Center as one of 72 hospitals capable of performing unrelated allogeneic BMT transplants from the world's pool of potential donors.

Summary

Allogeneic and autologous bone marrow transplantation has been performed in Hawaii since 1978 for leukemia, lymphoma, aplastic anemia, and advanced breast cancer. The numbers for each group are relatively small and the disease stages are diverse. Our program has been recognized and approved by the various national organizations, and we hope to continue to provide this treatment alternative to appropriate candidates.

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